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| <div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>(21) International Application Number: PCT/GB97/02358</p> <p>(22) International Filing Date: 1 September 1997 (01.09.97)</p> <p>(30) Priority Data:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%;">9618277.9</td> <td style="width: 30%;">2 September 1996 (02.09.96)</td> <td style="width: 40%;">GB</td> </tr> <tr> <td>9700896.5</td> <td>17 January 1997 (17.01.97)</td> <td>GB</td> </tr> </table> <p>(71) Applicant (for all designated States except US): THE MANCHESTER METROPOLITAN UNIVERSITY [GB/GB]; All Saints Building, All Saints, Manchester M15 6BH (GB).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): D'SILVA, Claudius [GB/GB]; 23 Chiltern Drive, Hale/Altringham, Cheshire WA15 9PL (GB).</p> <p>(74) Agents: EVANS, David, Charles et al.; F.J. Cleveland & Company, 40-43 Chancery Lane, London WC2A 1JQ (GB).</p> </div> <div style="width: 48%;"> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> </div> </div> | | | 9618277.9 | 2 September 1996 (02.09.96) | GB | 9700896.5 | 17 January 1997 (17.01.97) | GB |
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| <p>(54) Title: S-BLOCKED GLUTATHIONES</p> <div style="text-align: center; margin: 20px 0;"> </div> | | | | | | | | |
| <p>(57) Abstract</p> <p>This invention concerns glutathione derivatives, and in particular their application in the suppression of pathogens. It has been discovered that certain glutathione derivatives are effective inhibitors of the growth of a range of cancer cell types, and certain micro-organisms. According to one aspect of the present invention there is provided a glutathione having structure (I). Compounds based upon this general structure are disclosed which are active against parasitic infectious agents such as T. Brucei and L. Donovan. Further compounds are disclosed which are active against cancer cells.</p> | | | | | | | | |

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S-Blocked Glutathiones

This invention concerns glutathione derivatives, and
5 in particular their application in the suppression of
pathogens.

Illness may be caused by many agents. Bacterial
infections are caused by micro-organisms which
10 multiply rapidly and cause a number of diseases.
Parasites are organisms which live in or on a host and
feed off the host. Cancers are evident by the
uncontrolled multiplication of cells in the body. The
cancer may be localized, such as breast cancer, or
15 systemic such as leukaemia.

The treatment of the illnesses caused by the
aforementioned agents has been the subject of much
research, and many different approaches. One approach
20 involves targeting the cells which cause the disease
and destroying them or disrupting their ability to
multiply.

For such an approach to be successful the agent or
25 drug used to attack the diseased cells should not harm
significantly other healthy cells. Thus such an

approach requires an understanding and identification of the biochemical processes carried out in cells, and the targeting and disruption of specific processes which are unique to the diseased cells.

5

Such an approach involves the use of the cytotoxic compound methylgloxal which is produced in the cells of certain organisms. A build up of methylgloxal in the cell up to cytotoxic levels will, of course, result in cell death. By inducing a build up of methylgloxal, significant growth inhibition effects have been seen in tumour cells, *Escherichia coli*, *Saccharomyces cerevisiae* and *Leishmania donovani*.

15 The build up of methylgloxal may be promoted by the inhibition of glyoxalase I (GLI) enzyme. A wide range of inhibitors of GLI are known and these include substrate or product analogues and mechanism-based inhibitors.

20

Glutathione (γ -glutamylcysteinylglycine) fulfils a variety of roles vital to life processes. It functions as a co-enzyme, co-substrate, substrate or part of the substrate architecture. S-blocked glutathiones have been shown to be potent inhibitors of GLI in vitro and this has led to a search for particular S-blocked

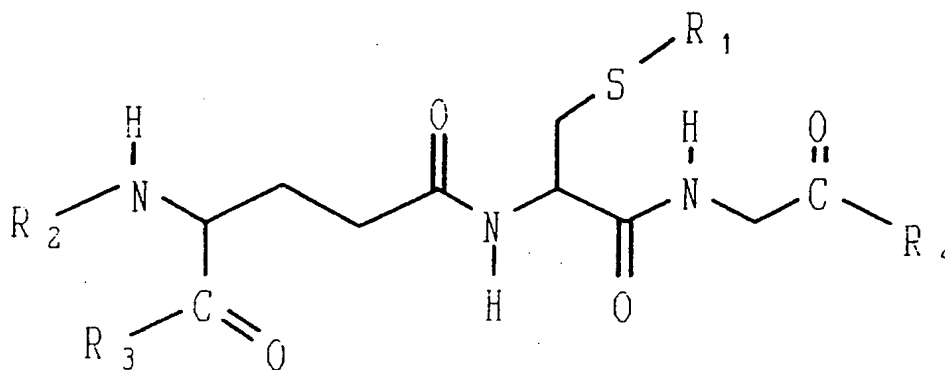
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glutathiones which may have therapeutic effect.

A general procedure for the preparation of the monoglycyl and dimethyl ester and amide derivatives of
5 S-(4-bromobenzyl)glutathione has been described by the inventor in Biochem. J. (1990) 271, pp167-169.

The inventor has discovered that certain glutathione derivatives are effective inhibitors of the growth of
10 a range of cancer cell types, and certain micro-organisms.

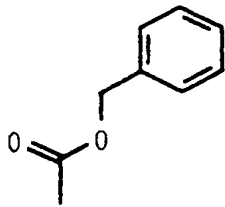
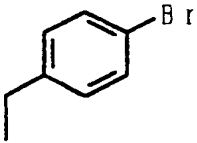
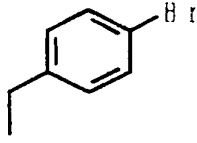
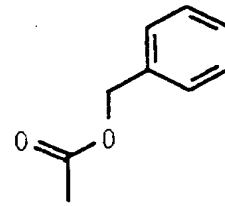
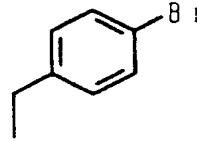
According to one aspect of the present invention there is provided a glutathione having the following
15 structure:-

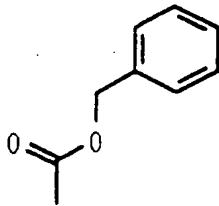
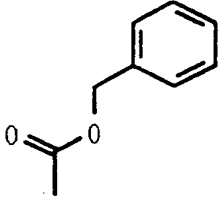
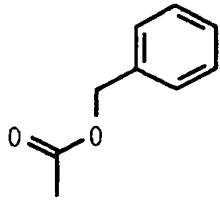
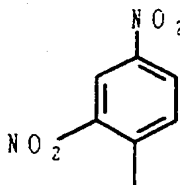


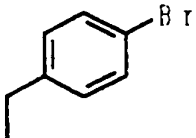
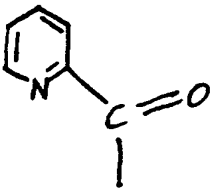
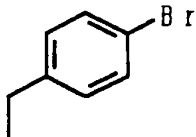
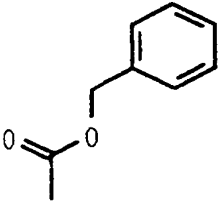
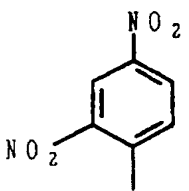
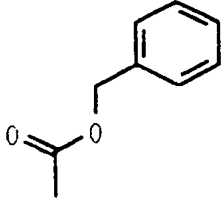
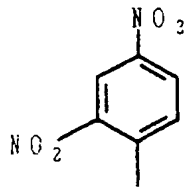
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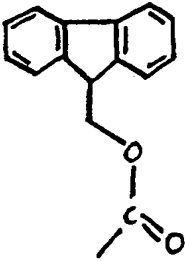
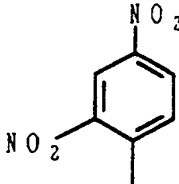
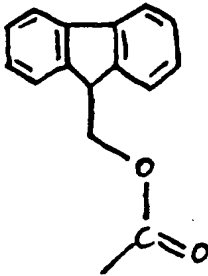
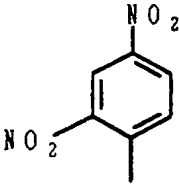
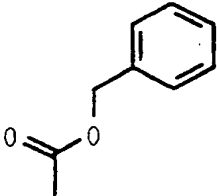
Where R₁-R₄ may be configured as shown in the following:

5

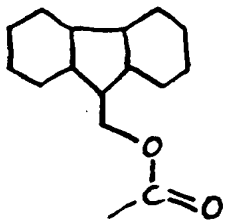
| LABEL | R ₂ | R ₁ | R ₄ | R ₃ | MW |
|-------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------|----------------|-------|
| CD4 |  |  | OMe | OMe | 638.5 |
| CD6 | CH ₃ CO |  | OH | OH | 545 |
| CD7 |  |  | OMe | OH | 624 |

| CD8 |  | CH ₂ -COOEt | OH | OH | 527 |
|-------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------|----------------|-----|
| CD10 |  |  | OMe | OMe | 692 |
| LABEL | R ₂ | R ₁ | R ₄ | R ₃ | MW |
| CD13 | H |  | OH | OH | - |

| | | | | | |
|------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------|-----|-----|
| CD16 | CHO |  | OH | OH | 504 |
| CD17 |  |  | NH ₂ | OH | 576 |
| CD19 |  |  | OMe | OH | 621 |
| CD20 |  |  | OMe | OMe | 635 |

| | | | | | |
|------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----|-----|-----|
| CD42 |  |  | OMe | OH | 708 |
| CD43 |  |  | OMe | OMe | 722 |
| CD46 |  | -CH ₂ -CO ₂ Et | OMe | OMe | 555 |

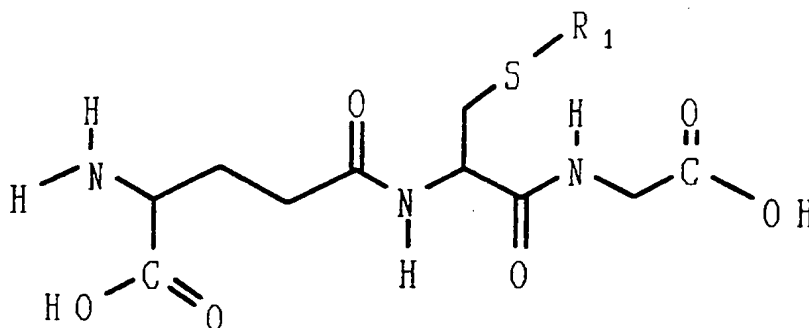
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| | | | | | |
|------|--------------------|------------------------------------------------------------------------------------|-----|----|-----|
| CD48 | CH ₃ CO |  | OMe | OH | 556 |
|------|--------------------|------------------------------------------------------------------------------------|-----|----|-----|

- CD7 has been found to be an effective inhibitor of Trypanosomiasis and in particular T. Brucei S247. This compound is also active against Malaria. One particular advantage of this compound is that it is effective at inhibiting the cell growth of the organism without being toxic to red blood cells.
- CD13 is effective at the inhibition of growth of cancer cells, and in particular leukaemia, breast cancer or tumour cells.

According to another aspect of the invention there is provided a glutathione having the following general formula:-

5 Wherein R₁
is:-



10 CH₂CH=C(
CH₃)CH₂CH₂CH=C(CH₃)CH₂CH₂CH=C(CH₃)₂
TRANS TRANS TRANS
S-(farnesyl)glutathione CD37

The aforementioned glutathione derivatives may each be
provided in pharmaceutically acceptable compositions
15 for delivery to the human or animal body.

In another aspect of the invention there is provided
the use of any one of the foregoing compounds in the
treatment of cancer, or parasitic cellular
20 infestation.

In particular, according to one embodiment of the
present invention there is provided the use of CD13
and derivatives thereof in the treatment of cancer.
25

According to another embodiment there is provided the

10

use of CD19 and/or CD20 in the treatment of a
infection by a parasitic micro-organism.

In particular Cd19 is highly effective at low
5 concentrations against T. brucei (African sleeping
sickness), while CD 20 has no toxicity to red blood
cells. CD20 also has good activity against other
parasites such as L.donovani (oriental sore, Kala-
azar).

10

According to another aspect of the invention there is
provided the use of CD7 against malaria.

According to yet another aspect of the invention there
15 is provided the use of any one of compounds CD26-CD37
against cancer.

According to another aspect of the invention there is
provided the use of CD13, CD4, CD6 and CD 37 against
20 cancer, and in particular breast cancer, and more
particularly MCF7 cells.

Following is a description by way of example only of
methods of putting the present invention into effect
25 and examples demonstrating the activity of compounds
according to the present invention. The drawing is a

11

graphic representation of the results of the in vivo test described in example 1.

General method of production.

5



Reduced glutathione (1g, 3.26mM) is dissolved in H₂O (5ml) and 2M NaOH (3.3ml, 6.6mM) with stirring at room
10 temperature and under a nitrogen atmosphere. Ethanol (5-15ml) is then added to the cloud point whereafter RX (for example, aryl halide, 3.5mM dissolved in ethanol) is added portion-wise over about 30 minutes. The reaction is left to stir for 20 hours under
15 nitrogen.

If precipitation occurs during addition either more ethanol or more water is added to dissolve the material. At the end the reaction the acidity of the
20 mixture is adjusted to p 3.5 with 2M HCl and the mixture chilled to effect precipitation. The precipitate is then filtered, washed with water, dried and recrystallized from Ethanol/H₂O.

25 Pharmaceutical activity:

Example 1

12

Glutathione CD13 according to the present invention was tested in order to ascertain its inhibitory characteristics with respect to various cancer cell lines.

5

The compound was introduced to cell cultures and the concentration of cancer cells formed over a period of time was measured using standard techniques. The following table indicates the results for CD13 and another glutathione derivative "control" by way of comparison:-

10

| | Leukaemia lines | | Tumour cells | Breast Cancer cells |
|----------|------------------------|------------------------|------------------------|------------------------|
| | WEH1 3B | K562 | MAC 15A | MCF7 |
| Compound | conc. $\mu\text{g/ml}$ | conc. $\mu\text{g/ml}$ | conc. $\mu\text{g/ml}$ | conc. $\mu\text{g/ml}$ |
| Control | 36 | 54 | >100 | >100 |
| CD13 | 3.4 | 2.5 | 0.43 | 0.48 |

15

CD13 was tested in vivo on rodents with MAC 15A S/C Tumours by giving them a 20 mg/Kg daily dose for five days. The treatment resulted in a reduction in tumour size and a 45% reduction in tumour volume after 4 days. The effect of CD 13 in the above test is shown

20

13

in the graph of the drawings.

Example 2

- 5 The glutathione derivatives CD7 and CD 10 according to the present invention were tested for their activity against the parasites T.Brucei S247, L.donovani and T. cruzi.
- 10 The following table shows the mean estimation of growth of T.Brucei S247 in a 72 hour incubation in the presence of a control glutathione derivative and CD10 in various concentrations:-

15

| Compound | MIC @ concentration (μ M) | | | |
|----------|--------------------------------|------|-------|-------|
| | 30 | 10 | 3 | 1 |
| control | ++++ | ++++ | +++++ | +++++ |
| CD7 | 0 | ++++ | +++++ | +++++ |
| CD10 | 0 | ++++ | +++++ | +++++ |

20

The forgoing table shows that Compounds CD7 and CD10 exhibit complete inhibition of the growth of T.Brucei S247 over the specified period at concentrations of 30 μ M.

25

14

The following table shows the results of the inhibition of the growth of *L. donovani* and *T. Cruzi* by compounds CD7, CD10 according to the present invention and "control" by way of comparison, at various concentrations.

| Compound | % Inhibition of <u>L.donovani</u> @ conc. | | | % Inhibition of <u>T. Cruzi</u> @ conc. | | |
|----------|----------------------------------------------|------------------|------------------|--------------------------------------------|------------------|------------------|
| | 90 (μ M) | 30 (μ M) | 10 (μ M) | 90 (μ M) | 30 (μ M) | 10 (μ M) |
| control | 0 | 0 | 0 | 0 | 0 | 0 |
| CD7 | 0 | 0 | 0 | 0 | 0 | 0 |
| CD10 | T | T | 0 | T | T | T/0 |

10

The foregoing shows that compound CD10 shows good activity in the inhibition of growth of both *L. donovani* and *T. cruzi*.

15

Example 3:

20 Activity of compounds CD16-CD20 in Vitro.

| Compound | % inhibition @ concn. (μ M) |
|----------|----------------------------------|
| | |

15

5

10

| | 30 | 10 | 3 | 1 |
|------------|------|------|------|---|
| CD16 | | | | |
| T.cruzi | 11.0 | 0 | 0 | 0 |
| CD17 | | | | |
| T.cruzi | 7.0 | 4.0 | 0 | 0 |
| CD19 | | | | |
| T.brucei | 100 | 100 | 33.2 | 0 |
| CD20 | | | | |
| L.donovani | 13.5 | 1.9 | 0 | 0 |
| T.brucei | 100 | 64.5 | 0 | 0 |

Example 4:

Compound CD48 was tested for its activity against cancer, with the following results for a range of cancer types:

| Cancer | Human Ovarian carcinoma | Human lung carcinoma | Human colon carcinoma | Human myelogenous leukaemia | Mouse lymphoid neoplasm |
|-------------|-------------------------|----------------------|-----------------------|-----------------------------|-------------------------|
| Designation | A2780 | H-460 | BE | K562 | P388 |

16

| | μM | μM | μM | μM | μM |
|------|---------------|---------------|---------------|---------------|---------------|
| CD48 | >50 | >50 | 27.1 | 16.7 | 31.7 |

Example 5:

5

Compounds CD4, CD6, and CD 37 have also been found to be effective against various cancers, including breast cancer.

10 Example 6:

Compounds CD42 to 48 were tested for their activity against various parasitic infection agents and the results are shown in the following table:

15

| Comp ound | % INHIBITION OF T.BRUCI S247 | | | | %INHIBITION OF L. DONOVANI | | | |
|--------------|---------------------------------|------------------|-----------------|-----------------|-------------------------------|------------------|-----------------|-----------------|
| | 30 μM | 10 μM | 3 μM | 1 μM | 30 μM | 10 μM | 3 μM | 1 μM |
| CD42 | 100 | 100 | 0 | 0 | 1.2 | 0 | 0 | 0 |
| CD43 | 100 | 100 | 0 | 0 | T/O | 0 | 0 | 0 |
| CD44 | 100 | 100 | 100 | 63.2 | T/ 100 | 0 | 0 | 0 |

20

17

| | | | | | | | | |
|------|---|---|---|---|------|---|---|---|
| CD46 | 0 | 0 | 0 | 0 | 66.2 | 0 | 0 | 0 |
| | | | | | 3 | | | |

Key: T/0 = toxic to macrophages / parasites present.

T/100 = toxic to macrophages / no parasites
present.

5

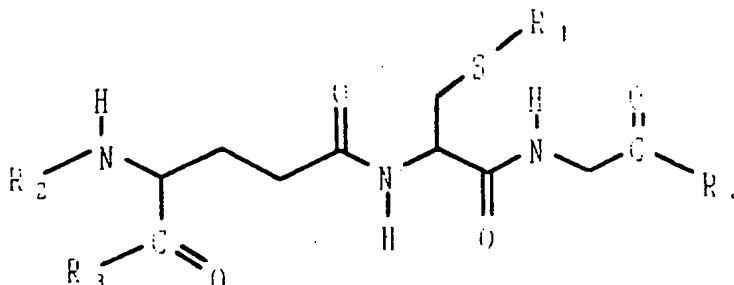
100+ = 100% inhibition when sampling for
haemocytometer count but parasites visible in
wells of 96-well plate under inverted mic.

10

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CLAIMS

1. A compound having the following general structure:-

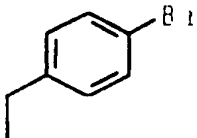
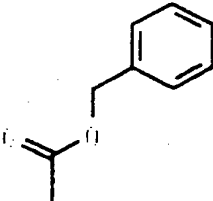
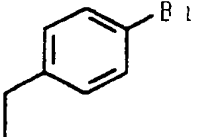
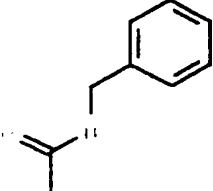


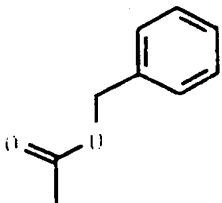
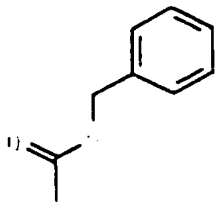
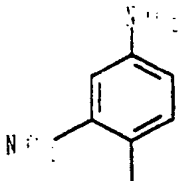
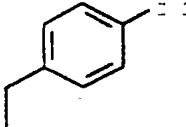
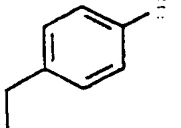
5

and wherein R_1 to R_4 are according to any one of the following rows in the table:

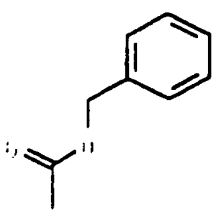
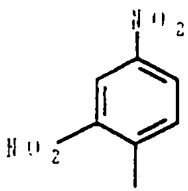
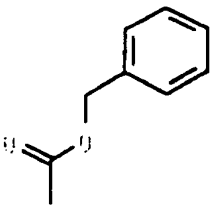
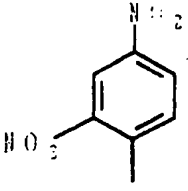
| LABEL | R_2 | R_1 | R_4 | R_3 |
|-------|-------|-------|-------|-------|
| CD4 | | | OMe | OMe |

10

| | | | | |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----|----|
| CD6 | CH_3CO |  | OH | OH |
| CD7 |  |  | OMe | OH |
| CD8 |  | $\text{CH}_2\text{-COOEt}$ | OH | OH |

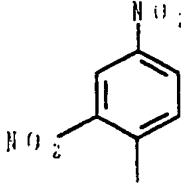
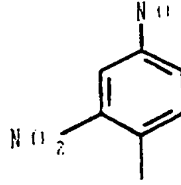
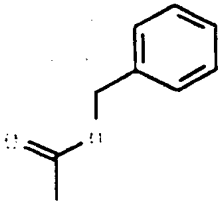
| | | | | |
|------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------|-----|
| CD10 |  |  | OMe | OMe |
| CD13 | H |  | OH | OH |
| CD16 | CHO |  | OH | OH |
| CD17 | |  | NH ₂ | OH |

21

| | | | | |
|------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|
| CD19 |  |  | OMe | OH |
| CD20 |  |  | OMe | OMe |
| CD37 | H | $\begin{aligned} &-\text{CH}_2\text{CH}=\text{C}(\text{CH}_3) \\ &)\text{CH}_2\text{CH}_2\text{CH}=\text{C}(\text{CH}_3) \\ &\text{CH}_2\text{CH}_2\text{CH} \\ &=\text{C}(\text{CH}_3)_2 \end{aligned}$ | OH | OH |

SUBSTITUTE SHEET (RULE 26)

22

| | | | | |
|------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----|-----|
| CD42 | |  | OMe | OH |
| CD43 | |  | OMe | OMe |
| CD46 |  | -CH ₂ -CO ₂ Et | OMe | OMe |

SUBSTITUTE SHEET (RULE 26)

23

| | | | | |
|------|--------------------|--|-----|----|
| CD48 | CH ₃ CO | | OMe | OH |
|------|--------------------|--|-----|----|

2. A pharmaceutically acceptable composition for
5 delivery to the human or animal body comprising a
compound according to claim 1.
3. A composition for the treatment of parasitic
infection, which composition comprises one or
10 more of CD7, CD19, CD20, CD42, CD43 or CD44
according to claim 1.
4. A composition for the treatment of
trypanosomiasis, and in particular infection by
15 T. Brucei, which composition comprises one or
more of CD7, CD19, CD20, CD42, CD43 and CD44
according to claim 1.
5. A composition as for the treatment of
20 Leishmaniasis, and in particular infection by L.
donovani, which composition comprises one or
more of CD20, CD42, CD43, CD44 and CD46 according

SUBSTITUTE SHEET (RULE 26)

to claim 1.

6. A composition for the treatment of cancer, which
composition comprises one or more of CD4, CD6,
5 CD13 and CD37 according to claim 1.

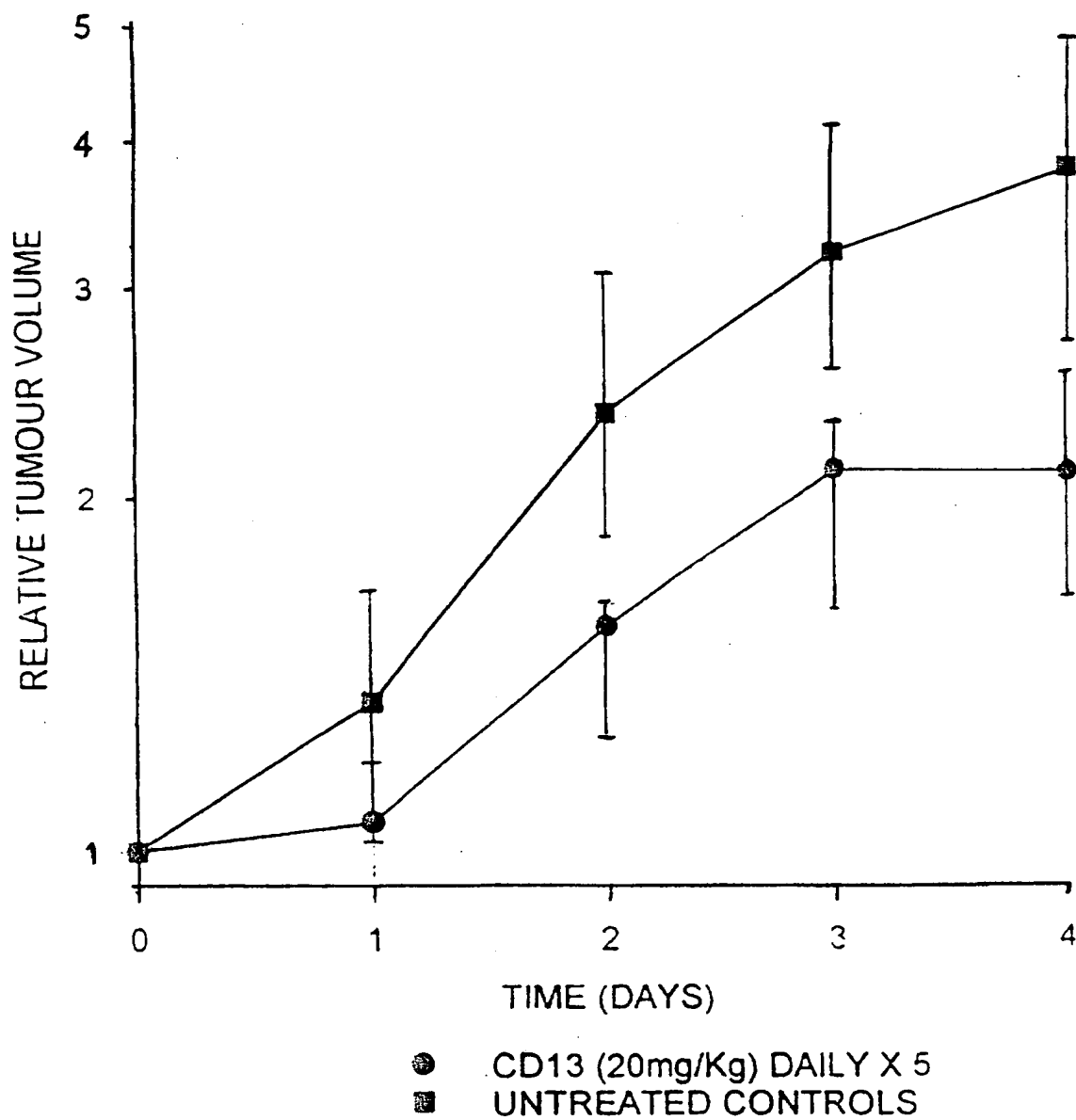
7. A method of treating a diseased human or animal
comprising administering a pharmologically
effective amount of a composition as claimed in
10 claim 2.

8. A method of treating parasitic infection of a
human or animal comprising administering a
pharmologically effective amount of a composition
15 as claimed in any of claims 3,4 and 5.

9. A method of treating cancer in a human or animal
comprising administering a pharmologically
effective amount of a composition as claimed in
20 claim 6.

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MAC15A S/C TUMOURS TREATED WITH CD13 DAILY



INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/GB 97/02358

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/02 A61K38/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X | R.VINC ET AL.: "Studies on the Inhibition of Glyoxalase I by S-Substituted Gluthationes" J.MED.CHEM., vol. 14, no. 5, 1971, page 402-4 XP002044716 see paragraph 1; example 39; table 1 --- | 1,6-9 |
| X | A.AL-TIMARI ET AL.: "Inhibition of mammalian glyoxalase I (lactoylglutathione lyase) by N-acylated S-blocked glutathione derivatives as a probe for role of the N-site of glutathione in glyoxalase I mechanism" BIOCHIM.BIOPHYS.ACTA, vol. 86, no. 1, 1986, pages 160-8, XP002044717 see tables 12,5 --- -/- | 1,6-9 |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

27 October 1997

Date of mailing of the international search report

13. 11. 97

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INTERNATIONAL SEARCH REPORT

Intern. Appl. No.

PCT/GB 97/02358

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X | A.AL-TIMARI ET AL.: "Inhibition of glutathione derivatives of bovine liver glyoxalase II (Hydroxyacylglutathione hydrolase) as a probe of the N- and S-sites for substrate binding" BIOCHIM.BIOPHYS.ACTA, vol. 870, no. 2, 1986, page 219-25 XP002044718 see example 2; table I --- | 1,6-9 |
| A | S.J.NORTON ET AL.: "Inhibitors and inhibition of mammalian glyoxalase II activity" BIOCHEM.SOC.TRNS., vol. 21, no. 2, 1993, pages 545-9, XP002044719 --- | |
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Information on patent family members

Intern. Appl. No.

PCT/GB 97/02358

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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